Exenatide (Byetta) as a novel treatment option for type 2 diabetes mellitus

Aaron Bond, PharmD

Exenatide is the first drug in the incretin mimetic class and is indicated for treatment of type 2 diabetes mellitus. Although structurally similar to the native glucagon-like peptide, this synthetic form has a much longer duration of action. Randomized trials have shown exenatide to be efficacious in improving glycemic control when combined with either metformin or a sulfonylurea. The dose is initially 5 mcg subcutaneously twice daily and may be titrated to 10 mcg subcutaneously twice daily to achieve better diabetes management. Nausea, vomiting, and diarrhea were the most common adverse events reported with exenatide therapy. Exenatide is not associated with hypoglycemia, which may provide advantages over adding insulin to a sulfonylurea or metformin.

The American Diabetes Association estimates that 17 million people in the USA have type 2 diabetes (1). Currently, the first-line oral agents for type 2 diabetes are metformin and sulfonylureas. Other therapeutic options include thiazolidinediones and insulin. Despite best efforts, monotherapy or combination therapy of metformin and a sulfonylurea fails in many patients. This presents a problem because many second- and third-line agents may cause weight gain, hypoglycemia, and other adverse effects. Exenatide (Byetta) is the first in a new class of incretin peptide mimetics (glucagon-like polypeptide-1 [GLP-1] receptor agonists) available in the USA. It was approved by the Food and Drug Administration (FDA) in April 2005 for adjunctive glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea (2).

PHARMACOLOGY AND PHARMACOKINETICS

Exenatide's action is due to its structural similarity to GLP-1. The glucoregulatory activities include enhancing glucose-dependent insulin synthesis from pancreatic beta cells, decreasing glucagon production, and slowing gastric emptying time. GLP-1 is a naturally occurring hormone that is released from the gastrointestinal tract and enhances the glucose-dependent insulin response (3). Trials using native GLP-1 showed no clinical benefit due to its very short half-life (<1 min) (4, 5). Exenatide is the synthetic version of exendin-4, an incretin hormone originally found in the saliva of the Gila monster *Heloderma suspectum*. It has a greater potency and a longer duration of action than the native GLP-1 when administered subcutaneously (5).

Exenatide's absorption reaches median plasma concentration 2.1 hours after subcutaneous injection. The drug is primarily eliminated by glomerular filtration followed by proteolytic degradation, with an elimination half-life of 2.4 hours. Exenatide's elimination is not appreciably reduced in mild to moderate renal impairment, and dosage adjustment is not warranted. In end-stage renal disease, its elimination is significantly reduced; its use in this condition is contraindicated (2).

CLINICAL TRIALS

Three phase III clinical trials have been published comparing the use of exenatide as adjunctive therapy to metformin alone, sulfonylurea alone, or the combination. All studies were conducted over a 30-week period and were placebo controlled. Two of the studies were triple-blinded, and the third study was double-blinded.

In combination with metformin alone

DeFronzo et al compared exenatide in type 2 diabetic patients being treated with metformin monotherapy in a multicentered, randomized, triple-blinded, placebo-controlled study (6). Patients were between the ages of 19 and 78 years, with a mean age of 53. For inclusion, patients had to receive a metformin dose of ≥1.5 g/day for the 3 weeks prior to screening. Patients who had used any other diabetes agents or medications that would alter plasma glucose (e.g., corticosteroids) within the prior 3 months were excluded. The primary endpoints of the study were glycemic control measured by hemoglobin A_{1C} (HbA_{1C}) and safety. The secondary endpoint was the percentage of patients with an HbA_{1C} ≤7%.

Four treatment arms were studied: metformin alone (two placebo arms), metformin and exenatide 5 mcg twice daily, and metformin and exenatide 10 mcg twice daily (5 mcg titrated to

From the Department of Pharmacy Services, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Aaron Bond, PharmD, Department of Pharmacy Services, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246 (e-mail: RoberBo@BaylorHealth.edu).

10 mcg after a 4-week run-in). The intention-to-treat population—that is, all patients who received one dose of medication—comprised 336 subjects. After 30 weeks, 272 (81%) had completed the study, and 64 patients had withdrawn. Withdrawal rates were not statistically significant across the treatment arms. Baseline HbA_{1C} across all treatment groups was 8.2%. Both exenatide treatment arms showed significant reduction in HbA_{1C}, with an overall $P < 0.001$. The 5-mcg treatment group showed a 0.4 ± 0.1% reduction and the 10-mcg group showed a 0.8 ± 0.1% reduction in HbA_{1C} at week 30. Baseline body weight across treatment arms was approximately 100 kg. Those in the exenatide 5 mcg group had a mean weight change of –1.6 ± 0.4 kg ($P \leq 0.05$), and those in the 10-mcg arm had a mean change of –2.8 ± 0.5 kg ($P \leq 0.001$). Weight loss was seen regardless of whether the subject had a body mass index >30 kg/m^2 (6).

In combination with a sulfonylurea alone

Buse et al evaluated exenatide versus sulfonylurea monotherapy in a multicenter, randomized, triple-blinded, placebo-controlled study (7). Patients were between the ages of 22 and 76 years, with a mean age of 55. For inclusion, patients had to be treated with maximally effective doses of sulfonylureas for the 3 weeks prior to screening. Patients who had used any other diabetes agents or medications that would alter plasma glucose within the prior 3 months were excluded.

All patients entered a 4-week placebo lead-in period in an effort to standardize therapy. Sulfonylurea therapies included glimepiride 4 mg/day, glipizide 20 mg/day, glipizide XL 10 mg/day, glyburide 10 mg/day, micronized glyburide 6 mg/day, chlorpropamide 350 mg/day, and tolazamide 500 mg/day. The sulfonylurea dose could be reduced by 50% in the event of a documented hypoglycemic event or two undocumented suspected events. The primary endpoints of the study were glycemic control measured by HbA_{1C} and safety.

Four treatment arms were studied: sulfonylurea alone (two groups), sulfonylurea and exenatide 5 mcg twice daily, and sulfonylurea and exenatide 10 mcg twice daily (5 mcg titrated to 10 mcg after 4 weeks). All treatment arms were initially started on either exenatide 5 mcg twice daily or placebo, and after 4 weeks one treatment arm was increased to 10 mcg twice daily. After 30 weeks, the intention-to-treat population comprised 377 subjects, of whom 260 (69%) completed the study and 117 withdrew. Withdrawal rates were not statistically significant across the treatment arms but were higher in the placebo group because of lack of glucose control. The sulfonylurea class medications used were glipizide (45%), glyburide (33%), glimepiride (20%), tolazamide (1%), and chlorpropamide (0.3%). Baseline HbA_{1C} across all treatment groups was 8.6%.

Both exenatide treatment arms showed significant reduction in HbA_{1C}, with an overall $P < 0.001$. The 5-mcg treatment group showed a 0.46 ± 0.12% reduction in HbA_{1C}, and the 10-mcg group showed a 0.86 ± 0.11% reduction in HbA_{1C}. Baseline body weight across treatment arms was approximately 96 kg. Those in the exenatide 5 mcg group lost an average of 0.9 ± 0.3 kg (NS vs placebo), and those in the 10-mcg group lost an average of 1.6 ± 0.3 kg ($P < 0.05$ vs placebo). No cases of severe hypoglycemia were reported. Overall, the incidence of mild to moderate hypoglycemia was 36% in the 10-mcg group, 14% in the 5-mcg group, and 3% in the placebo arms. Only one subject withdrew due to hypoglycemia (7).

In combination with metformin and a sulfonylurea

Kendall et al evaluated the effects of exenatide compared with metformin and a sulfonylurea for treatment of type 2 diabetes in a multicenter, randomized, double-blinded, placebo-controlled trial (8). Patients were between the ages of 19 and 78 years, with a mean age of 53. For inclusion, patients had to be on a metformin dose of ≥1.5 g/day for the 3 weeks prior to screening, using either the maximally effective sulfonylurea dose or the minimal recommended dose. Patients who had used any other diabetes agents or medications that would alter plasma glucose within the prior 3 months were excluded. The primary endpoints of the study were glycemic control measured by HbA_{1C} and safety.

Four treatment arms were studied: metformin and a sulfonylurea with placebo (two groups); metformin, a sulfonylurea, and exenatide 5 mcg twice daily; and metformin, a sulfonylurea, and exenatide 10 mcg twice daily (5 mcg titrated to 10 mcg after a 4-week run-in). Of the 773 subjects in the intention-to-treat population, 593 (81%) completed the study and 180 withdrew. Withdrawal rates were not statistically significant across the treatment arms. Baseline HbA_{1C} across all treatment groups was 8.2%. Both exenatide treatment arms showed significant reduction in HbA_{1C}, with an overall $P < 0.001$. The 5-mcg treatment group had a 0.5 ± 0.2% reduction in HbA_{1C} and the 10-mcg group had a 0.6 ± 0.2% reduction in HbA_{1C}. Baseline body weight across treatment arms was approximately 100 kg. At 30 weeks, both exenatide treatment arms showed a mean weight change of –1.6 ± 0.2 kg compared with –0.9 ± 0.2 kg with placebo (8).

CONTRAINDICATIONS AND WARNINGS

Exenatide is contraindicated in patients with known hypersensitivity to this product or any of its components (2).

Exenatide is not a substitute for insulin in insulin-requiring patients. Exenatide should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. The concurrent use of exenatide with insulin, thiazolidinediones, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors has not been studied.

Exenatide is not recommended in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). In patients with end-stage renal disease receiving dialysis, single doses of exenatide 5 mcg were not well tolerated due to gastrointestinal side effects.

Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. Therefore, the use of exenatide is not recommended in patients with severe gastrointestinal disease (2).

Exenatide is listed as pregnancy category C. There are no adequate studies in pregnant women; however, in mice, ex-

Table 1. Frequent treatment-emergent adverse events (≥5% incidence and greater incidence with Byetta treatment) excluding hypoglycemia*

	Incidence (%)	
Adverse event	Placebo (N = 483)	Exenatide (N = 963)
Nausea	18	44
Vomiting	4	13
Diarrhea	6	13
Feeling jittery	4	9
Dizziness	6	9
Headache	6	9
Dyspepsia	3	6

*Reprinted from reference 2. Based on three 30-week placebo-controlled clinical trials (6–8).

Table 2. Incidence of hypoglycemia by concomitant antidiabetic therapy*

			With metformin and SFU	
Exenatide dose	With metformin	With SFU	Minimum SFU dose	Maximum SFU dose
None (placebo)	5.3%	3.3%	10%	15%
5 mcg twice daily	4.5%	14.9%	16%	22%
10 mcg twice daily	5.3%	35.7%	21%	35%

*From references 6–8. Hypoglycemia was defined as blood glucose <60 mg/dL and symptoms, or symptoms without a blood glucose level.
SFU indicates sulfonylurea.

enatide has been shown to reduce fetal and neonatal growth and to have skeletal effects at the 20 mcg/day recommended maximum dose.

ADVERSE EVENTS

In all three clinical trials, the most frequent adverse events were mild to moderate in nature, with nausea being the most prevalent (6–8) *(Table 1).* As therapy continued, the nausea appeared to decline in severity and was dose-dependent. Hypoglycemia was defined as a blood glucose level <60 mg/dL and symptoms, or symptoms without an accompanying blood glucose level. A relatively low number of episodes of hypoglycemia were reported, all in the trial that compared exenatide with a sulfonylurea alone *(Table 2).*

DOSING AND ADMINISTRATION

The recommended starting dose for the adjunctive treatment of type 2 diabetes mellitus is 5 mcg per dose administered subcutaneously twice daily 60 minutes before the morning and evening meals. If response is inadequate, the dose may be increased to 10 mcg twice daily after 1 month of therapy. The dose may be administered subcutaneously in the thigh, abdomen, or upper arm. No dose adjustment is needed for patients currently on metformin; patients on a sulfonylurea may need a dose reduction to reduce the risk of hypoglycemia.

Exenatide is available in two 250 mcg/mL prefilled pen-injectors: a 5-mcg/dose 1.2 mL pen and a 10-mcg/dose 2.4 mL pen. Each pen contains 60 doses.

Table 3. Cost of exenatide and formulary second- or third-line agents for type 2 diabetes*

Drug	Cost per vial/ tablet	Cost per month
Exenatide 5 mcg twice daily	$155.82	$155.82
Exenatide 10 mcg twice daily	$182.85	$182.85
Rosiglitazone 2 mg twice daily	$1.92	$115.60
Rosiglitazone 4 mg daily	$2.75	$82.52
Rosiglitazone 4 mg twice daily	$2.75	$165.00
Rosiglitazone 8 mg daily	$5.09	$305.66
Repaglinide 0.5 mg, 1 mg, 2 mg	$1.11	$66.60–$133.20
Insulin glargine	$62.28	Variable
Insulin NPH	$27.67	Variable

*Cost based on wholesale acquisition cost.

DRUG INTERACTIONS

Exenatide has been shown to reduce gastric emptying time, which in turn may affect the rate of absorption of oral medications. Oral medications that are dependent on gastric emptying for bioavailability should not be given within 1 hour of exenatide injections.

ECONOMIC ISSUES

In the pharmacy at Baylor University Medical Center, the acquisition costs of the 5-mcg and 10-mcg pens are $155.82 and $182.85, respectively. Thus, the annual cost of exenatide would be approximately $1800 to $2200 for the adjunctive treatment of type 2 diabetes. Both of the prefilled pens are a 30-day supply of medication. Needles are not included with the prefilled pens and must be considered in determining the cost to the patient. *Table 3* compares the cost of exenatide with that of other second- and third-line agents.

SUMMARY AND RECOMMENDATION

Exenatide is the first in the incretin mimetic class that offers another treatment for patients with type 2 diabetes. Clinical trials have shown a benefit to adding exenatide to metformin and sulfonylureas. The weight loss seen with exenatide is also an advantage over most of the current treatments; however, it is difficult to determine if nausea plays a role in weight loss. The concern for exenatide's use in type 2 diabetics is the reduction in gastric emptying. Oftentimes patients with diabetes have gastroparesis, and exenatide may compound this disease complication, but more studies are forthcoming. Also of interest is the preservation of the beta cells of the pancreas and the conversion of non–insulin-secreting cells to insulin-secreting cells in vitro. Studies are ongoing that will hopefully elucidate

the true effect that exenatide has on the beta cells. Exenatide is more expensive than other third-line agents but is a novel class for treatment of type 2 diabetes and may offer advantages with respect to side effects and weight loss.

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